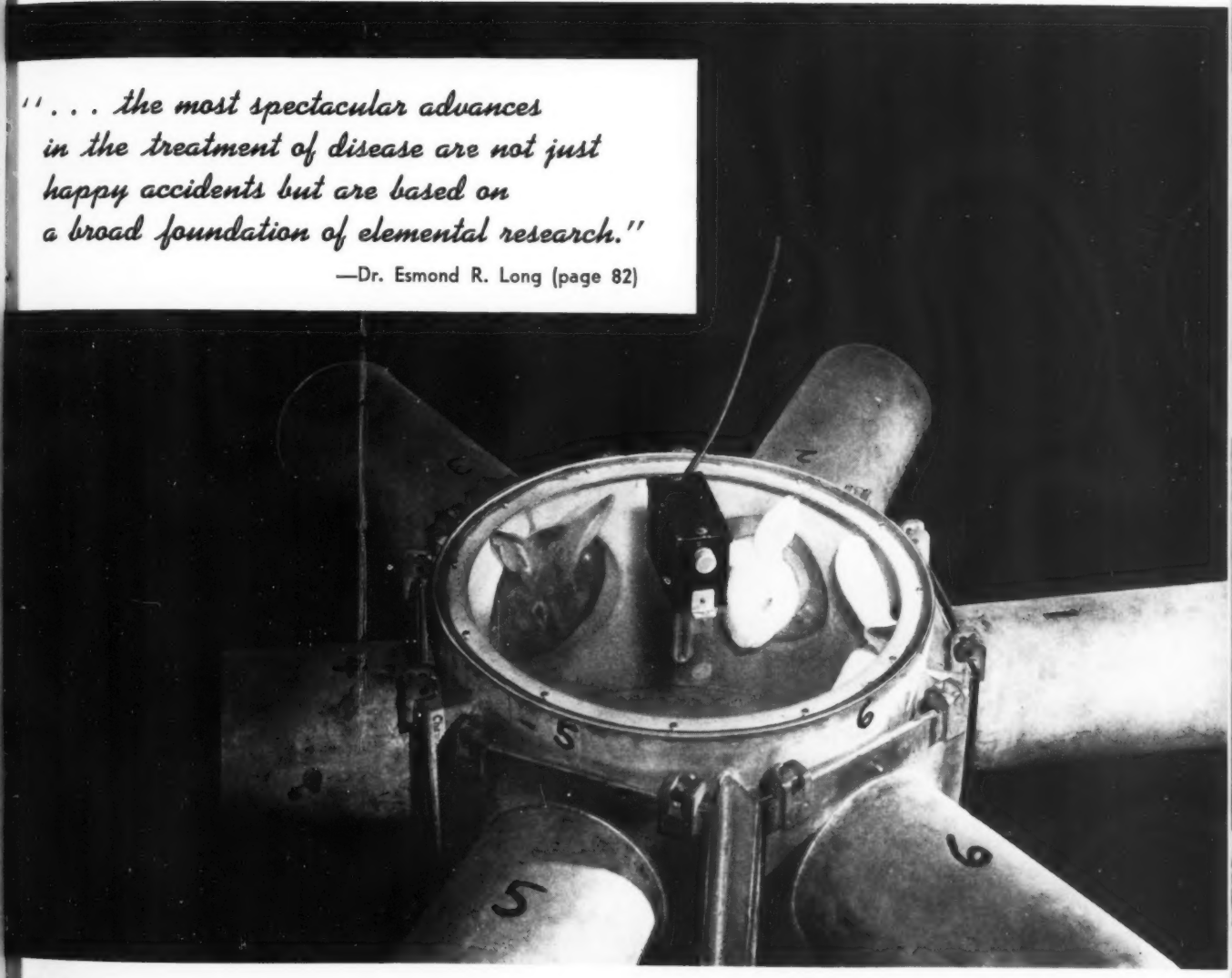
bulletin

NATIONAL TUBERCULOSIS ASSOCIATION

JUNE 1958

". . . the most spectacular advances in the treatment of disease are not just happy accidents but are based on a broad foundation of elemental research."

—Dr. Esmond R. Long (page 82)



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EDITORIAL

The Value of Basic Research

by Dr. Esmond R. Long

The satellite age has pointed up the importance of basic research. Theoretical physics and higher mathematics are no longer the concern of the abstract scientist alone. They have become a recognized and vital part of progressive programs of research, and indeed an element of desperate necessity in holding the line in a fast-widening perimeter of national defense.

There is nothing fundamentally different about medical research that sets it apart from the mathematical and related sciences with respect to basic and applied investigation. Educators and investigators themselves have always recognized that most apparent spectacular advances in the understanding and treatment of disease are not just happy accidents, but are based on a broad foundation of pertinent elemental research. The justly acclaimed Salk vaccine is a case in point. Without fundamental investigation on the culture of the infantile paralysis virus, the vaccine itself could not have been developed. In its wisdom some years ago, the Nobel Prize committee awarded this distinguished laurel to the patient group of investigators who learned how to propagate the potent virus of the disease in tissue culture outside of the body, without great concern about the ultimate use of their finding.

In the field of tuberculosis, isoniazid is another striking example. The chemical compound was discovered almost fifty years ago by a pair of organic chemists in a Vienna laboratory devoted to pure science. In the succeeding years a respectable body of information accumulated on the use of similar compounds in organic synthesis—synthesis for any purpose. When the chemotherapeutic potency of isoniazid was discovered—in a comprehensive program that took no chance of overlooking a possibly useful product, and which itself was based on an abundance of fundamental bacteriologic and pharmacologic research—it was apparent to all thoughtful laboratory chiefs that basic investigation of the kind that led to isoniazid was a necessity for future progress.

Research administrators, too, are quite aware of the essential role of basic study. In industrial, philanthropic, and governmental subsidies, provision is being made on a steadily increasing scale for fundamental research in the medical sciences. As a consequence, the volume of investigative results published has become enormous, and with it, and the inevitable race for personal recognition, has come a danger—the hazard of superficiality and the publication of a multitude of unverified findings.

In the current emphasis on basic research, it is essential that selection be based on quality rather than quantity, and certainly on truth rather than on an obviously pragmatic application. The experience of centuries has shown that practical use will be made eventually of every discovery that represents a fact. In the field of tuberculosis research, an unlimited amount of fundamental studies are still to be made. One thinks at once of the mechanism of antimicrobial action, the causes of bacterial virulence, the curious phenomenon of disease of tubercle bacilli themselves, and the innumerable ramifications of the nature of resistance in men. Imagination and tireless industry are necessary to keep up with the prospect. One thing sure is that the demands of the future will be insatiable and that good use will be found for every established finding.

The correlation of basic facts and the ensurance of their accessibility are serious problems of our time, which are being met, fortunately, by applied research in library administration. Communication is the life blood of science. The cooperation it establishes among scientists, and their own satisfaction in recognized accomplishment, are rewards on which we may count with some confidence for the needed investigators in the years ahead.

bulletin

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What Are the Needs in Tuberculosis Research?

by Roger S. Mitchell M.D.

While many of us advocate TB research in principle, we are often unaware of the planning and the work involved in such projects, and of the areas that particularly need investigation

At a tuberculosis association board meeting not long ago there was a discussion about the possibility of putting the association's money into a local medical research project. There seemed to be great enthusiasm for the principle of supporting research. Later, in discussing details, it was learned that the money was to be used to pay a technician's salary, to buy certain chemicals, and to pay for travel expenses of the principal investigator. Several well-meaning lay members of the board objected to the use of the association's money for these purposes: "We want to put our money into *research,* not into such mundane things."

Many persons who are asked to contribute money for medical research are unaware of what constitutes the planning and the performance of such work. Pitfalls in making generalizations are common, but it may be possible to clarify this situation somewhat.

In order to perform research, a physical plant—a building containing laboratories, offices, and various kinds of equipment, with heat, light, janitor services, and other utilities—must first be available. Equipment may be permanent or expendable. The permanent equipment varies widely, depending on the nature of the research to be undertaken—whether, for instance, it is in the field of microbiology, chemistry, or physiology. In any event, permanent equipment is apt to include many very expensive items, such as cold rooms, walk-in incubators, centrifuges, microscopes of various kinds, special analytical machines, and radioisotopic equipment. Expendable equipment includes glassware, reagents, animals, feed, etc.

In addition to the physical plant and equipment, personnel able and willing to initiate and carry out a research project must be available. First and foremost is the principal investigator, who plans, directs, and often carries out the project. Research assistants, associates, technicians, and laboratory helpers are necessary, plus secretaries, clerks, and, in the case of large medical centers, accountants and financial officers.

A research project must begin with an idea, or a so-called hypothesis. For instance, an investigator may formulate the idea that some chemical portion of tubercle bacilli might prevent, or reduce the seriousness of, tuberculous infection—i.e., immunize—when injected back into an animal or man. The investigator with such an idea must first review all the available medical literature on the subject. To do so, he must have access to a good medical library which has a close affiliation with other libraries. Frequently discussing his idea with colleagues in the same and other fields of science will help in planning his study. This may be done locally or at national scientific meetings.

As a plan of research evolves, it may become evident that new permanent equipment will be needed. New expendable supplies are continually needed, and new personnel especially competent in certain techniques may also be required.

An application for financial aid to one of several fund-granting agencies often becomes necessary. These applications must include detailed outlines of the purpose and plan of the study, previous research and knowledge on the subject by others, the past experience of the applicant, and the equipment and personnel available and required. The financial plans for the conduct of the investigation must undergo the scrutiny and approval of the parent organization before being submitted to the fund-granting agency.

After the fund-granting agency receives the application, a committee of well-qualified experts passes judgment

Dr. Mitchell is director, The Colorado Foundation for Research in Tuberculosis, and associate professor, University of Colorado School of Medicine. He received his B.A. and M.D. degrees from Harvard University and is a fellow of the American College of Physicians. Dr. Mitchell's article was solicited by the Governing Council of the National Conference of Tuberculosis Workers.

on the merits of the request. In due course, often after the grant has been activated, the work gets under way. As the work continues, progress reports to the fund-granting agency are required from time to time. Invariably, as such a study progresses, unforeseen new information and problems come to light. For instance, wholly unanticipated discoveries may be made. Obstacles to the discovery of the original goal frequently emerge. The study will usually take much longer than anticipated. The study opens new vistas, making study in other directions very desirable. Persons involved in the study may change employment or become ill. Other interferences with the even tenor of the work may occur. New information obtained from the study or from attendance at scientific meetings may result in a redirection of the effort. Preliminary reports of the investigation may be given at local or sectional scientific meetings. Later, more formal reports may be given at national meetings, and finally, reports of the work are submitted for publication in scientific journals. Renewals of grants-in-aid are sought where necessary at yearly intervals.

Having attempted to outline briefly the planning and the conduct of research, I would like now to dwell upon some of the specific problems *in tuberculosis* that to me, at any rate, appear to demand exploration.

A great argument continues about how best to grow or culture under artificial conditions the parasite that causes tuberculosis. Some present methods require as little as three weeks, while others require six to eight weeks. Some methods work well with material obtained from sputum or gastric washings, while others seem to work better when utilizing material obtained from lung tissue. The problem is made more difficult by the damage to tubercle bacilli from contact with drugs administered to the patients who are harboring them.

Much more knowledge is needed about the chemical make-up of tubercle bacilli, their fundamental nature, and the processes by which they breathe, multiply, and, most important, die. Under what circumstances will tubercle bacilli undergo mutation—that is, change in character? Are the new organisms—the atypical mycobacteria, or yellow bacilli—really mutants of true tubercle bacilli, or are they some separate, entirely different organisms? Incidentally, the disease that they cause is indistinguishable in most respects from true tuberculosis.

How do the drugs now available act against tubercle bacilli? Do they simply stop or slow down multiplication, or do they actually kill the bacteria?

How can we prevent or slow down the appearance of bacterial resistance to the action of drugs? Can we discover or create new drugs that will control bacteria which have become resistant to presently available agents?

At the Annual Meeting of the National Tuberculosis Association, held in Philadelphia, Pa., May 18-23, Dr. Mario M. Fischer took office as president of the NTA, Dr. Daniel E. Jenkins as president of the American Trudeau Society, and L. L. Taylor as president of the National Conference of Tuberculosis Workers. Since this issue of the *Bulletin* went to press before the meeting was held, a full report of the meeting will appear in July.

How can we speed up the testing of new, potentially valuable drugs? How can we speed up or otherwise simplify the tuberculin skin test?

In addition to new knowledge about tubercle bacilli, we need to know more about the part that the host—man—plays in the picture. What makes one person more immune to tuberculous infection than others? How does infection with tubercle bacilli produce the variable amount of immunity that is often manifest? Why do some persons acquire more immunity than others? Why does immunity seem to run in families? How can we measure this immunity against tuberculosis? How can we produce it artifically when desired? What other host factors are there that cause the wide variations in response to tuberculosis treatment that are seen in actual practice?

How frequently does relapse from tuberculosis occur after various forms of treatment, particularly after so-called modern drug treatment? Is it necessary to perform potentially serious lung operations on persons with empty spaces in their lungs—spaces that were previously tuberculous cavities but now appear entirely healed by all criteria, including many negative sputum examinations?

We need research particularly into the human factors that determine whether patients will follow the advice they are given. Perhaps the greatest problem in the management of tuberculous patients today is in persuading patients to do as they are instructed about treating their tuberculosis. How does one manage the chronic alcoholic with tuberculosis? How do we prevent departures from hospitalization against medical advice? How does one handle tuberculosis in our skid row population, which has little or no motivation to acquire or regain good health? Should there be compulsory isolation of recalcitrant infectious tuberculosis patients and, if so, under what circumstances?

It has been claimed by many authorities that we presently have the means of controlling practically all tuberculosis if these means were properly applied. On the other hand, there is much argument about how long to continue treatment and, most particularly, about the dosage of the available drugs. Surely we need agents more effective than presently available ones, for there is ample indication that no less than one year of continuous therapy is a minimal requirement, and indefinitely prolonged drug therapy is not infrequently recommended. It is our ambition to someday be able to effect a lasting cure in a month or two.

Using presently available agents, is it advisable to treat persons who are apparently well in every way but who have recently converted their tuberculin skin reactions from negative to positive? Should we not be looking for therapy that is 100 per cent rather than only 80 to 90 per cent effective?

In our search for new programs for Christmas Seal funds, have we not overlooked the bright prospects of an accelerated tuberculosis research program? Can we not afford more than 3 per cent of these funds for this purpose? My answer is an enthusiastic "yes."

STEPPING up the SEARCH

by Agnes Fahy

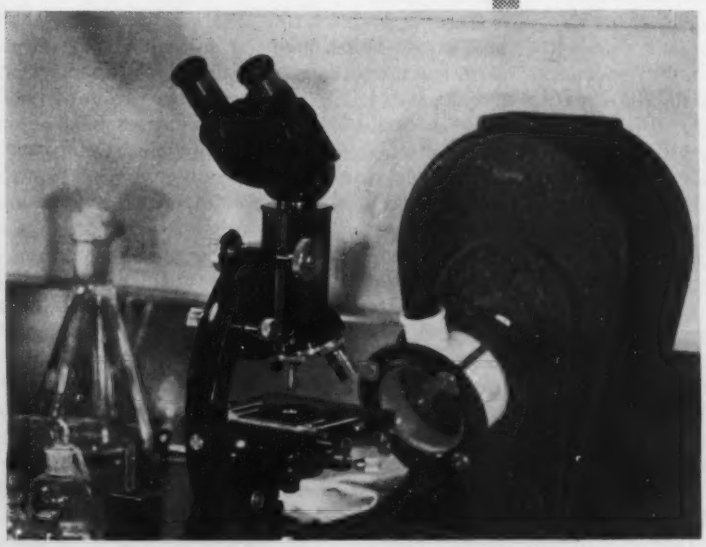
Science Writer, Public Relations Division
National Tuberculosis Association

Sixty-one applications for grants to aid medical research studies were received by the National Tuberculosis Association for the fiscal year beginning July 1. This was the largest number of applications in the 37-year-old history of the NTA grants-in-aid program. Support for the grants is from Christmas Seal funds and special bequests.

Of the 61 applications, 48 were approved by the Committee on Medical Research of the American Trudeau Society, which met in New York in February to review all applications. However, funds available for grants amounted to only $251,936, which was not sufficient to cover all the grants. (The sum included $210,000 from the NTA budget and $41,936 in contributions from affiliated associations for special projects.) Thus, at present, grants can be made to only 38 of the 48 investigators whose applications were approved. A total of $313,299 would have been necessary to make grants to all 48 investigators.

With the tightness of funds, the committee had another problem to face. Like everything else, the cost of research is going up. This is true, not so much in the basic budget of the investigator, but in overhead costs. Practically all medical research not sponsored by industry or a branch of government, or a foundation such as the Rockefeller Institute for Medical Research, is being carried on in laboratories connected with established hospitals or universities.

The institution where the research is conducted encounters certain expenses in connection with this research. There is a question of bookkeeping (checks are usually payable to the treasurer of the institution, not to the investigator); there are various housekeeping expenditures, for cleaning and the like. It is, therefore, customary for organizations or agencies making grants to include an item for overhead costs to the institution. For many years the NTA has made an overhead allowance of 8 per cent of the grant. Some granting bodies give an overhead as high as 25 per cent. In discussing this question this year, the Committee on Medical Re-



Thirty-eight investigators, supported by grants from the NTA, are carrying on intensive studies to increase our knowledge—and our control of tuberculosis

search decided it must adopt a more realistic policy and increased the overhead allowance to 15 per cent.

Of the 38 projects to be aided by grants as of July 1, six are new, and the rest are studies being continued from previous years. The new projects are marked with an asterisk. The studies fall into five broad categories—immunology, microbiology, pulmonary function, drug action, and clinical experience. No clear line of demarcation can be drawn among the categories. Obviously, studies of immunity involve work with the tubercle bacillus, and pulmonary-function studies are clinical as well as experimental. The projects, however, are grouped as nearly as possible according to the major interest of the investigator.

immunology

If immunity in tuberculosis followed a simple antigen-antibody pattern, we should know a great deal more about protecting people against tuberculosis than we now do. But because it is questionable whether antibodies (the production of which is the normal response of the body to the presence of antigens due to disease) play a role in immunity, and because the whole problem of resistance to tuberculosis is extraordinarily complex, the subject has attracted many scientific investigators since the tubercle bacillus was discovered more than 75 years ago. The approaches to the problem are varied, but the studies now under way are uncovering facts that will undoubtedly prove to be interrelated when immunity to tuberculosis is better understood.

Morgan Berthrong, M.D., Glockner-Penrose Hospital, Colorado Springs, Colo. A technique known as tissue culture is being used by Dr. Berthrong to test the theory that cell activity plays an important part in resistance to tuberculosis. In an exacting procedure, Dr. Berthrong infects monocyte cells extracted from the blood of guinea pigs with various strains of tubercle bacilli. He has observed that if the strain is of virulent organisms, the bacilli multiply so rapidly in the monocytes that eventually they literally burst the cells, an effect not observed with avirulent strains. He has further observed that cells from guinea pigs which have been immunized by the *inhalation* of BCG have greater ability to inhibit the multiplication of tubercle bacilli than cells from animals inoculated with BCG.

Leon R. Cole, M.D., University of Southern California Medical School, Los Angeles. Sensitivity to tuberculin is ordinarily due to the presence of tubercle bacilli in the person or animal tested. Dr. Cole, however, has succeeded in transferring sensitivity by transferring blood serum fractions from sensitized animals to unsensitized animals. This is known as passive transfer. Dr. Cole is attempting to identify the part of the serum responsible for carrying over the sensitivity and to determine the role of antibodies in causing reactivity in the second animal. He is also working on a blood test for active tuberculosis.

Max B. Lurie, M.D., The Henry Phipps Institute, University of Pennsylvania, Philadelphia. Native, rather than acquired, immunity is being studied by Dr. Lurie. He is seeking to identify constitutional factors that influence resistance or susceptibility to tuberculosis by studying rabbits bred true for resistance or susceptibility. Proper hormone balance, he has learned, is essential in keeping infection in check. More specifically, he has found that a high degree of thyroid activity increases, and a low degree decreases, resistance to tuberculosis. He now proposes to find out whether this is also true of certain other infections and how thyroid function exerts its influence.

Gardner Middlebrook, M.D., National Jewish Hospital at Denver. When artificial immunity is set in motion in experimental studies, it is usually by inoculation of the animal with BCG. A chance observation of Dr. Middlebrook's, however, indicated that immunity is enhanced if BCG is inhaled by the animals. Using an apparatus that permits air-borne infection with measurable amounts of bacilli, Dr. Middlebrook is planning to investigate more precisely what advantages inhalation of BCG may have over inoculation.

Sidney Raffel, M.D., Stanford University School of Medicine, Stanford, Calif. Long-range studies have led Dr. Raffel to the belief that the key to immunity in tuberculosis lies outside the antibody-antigen relationship. He is continuing to study the mechanism of acquired immunity and is inducing immunity in animals with a fraction of the tubercle bacillus which has been shown to have immunizing qualities. Dr. Raffel is also continuing to study allergy as evidenced by sensitivity to tuberculin and what, if any, its relationship is to im-

munity. He has recently collaborated with Dr. Leo Hollister, of the local Veterans Administration Hospital, in a clinical trial on the use of chlorpromazine, one of the tranquilizers, in tuberculosis patients, but has not found the results "startling."

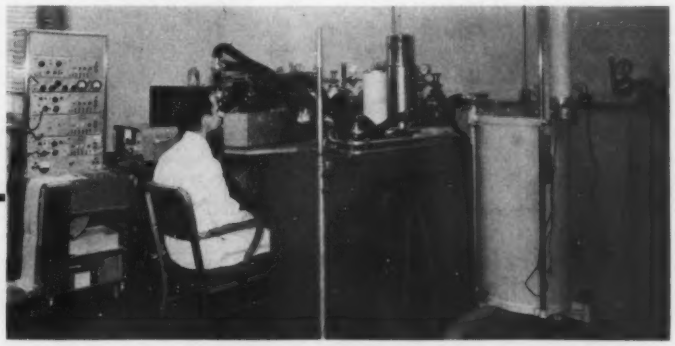
Florence B. Seibert, Ph.D., The Henry Phipps Institute, University of Pennsylvania, Philadelphia. Since identifying certain proteins as the key to the tuberculin reaction and then purifying PPD (Purified Protein Derivative), Dr. Seibert has devoted an increasing amount of time to studying the chemical components of the tubercle bacillus, particularly the proteins and polysaccharides. This has led naturally to the study of the role of these fractions in immunity. Dr. Seibert has come to believe that antibodies have an indirect, but important, role in immunity.

H. Stuart Willis, M.D., North Carolina Sanatorium System, Chapel Hill. A vaccine made from an avirulent strain of tubercle bacilli known as R_1 has been developed by Dr. Willis and has shown promise in experimental studies with animals. Dr. Willis is planning a number of tests this year to compare the vaccine with BCG.

Guy P. Youmans, M.D., Northwestern University School of Medicine, Chicago. A blood test, which in preliminary trials looks promising for the detection of active tuberculosis, has been developed by Dr. Youmans and associates. If further trials confirm the early promise, the test may be the long-awaited case-finding and diagnostic tool. The method employed is known as the gel double-diffusion technique. Agar, a gelatinlike substance made from seaweed, is used as the base for holding the antigen, which is made from virulent tubercle bacilli. After the antigen substance congeals in the tube, another layer of clear agar is pipetted into the tube, which is then filled with blood serum from the patient to be tested. If tuberculosis antibodies are present in the serum, a cloudy band of precipitation is formed as antibody meets antigen near the center of the tube.

***Abraham I. Braude, M.D., University of Pittsburgh School of Medicine, Pittsburgh.** One of the newer tools at the disposal of scientists, the isotope, is being employed by Dr. Braude to study the action of tuberculin in individuals who react to it. Dr. Braude plans to label tuberculin with radiochromium to find out whether the liver removes PPD from the blood more rapidly in resistant animals than in tuberculin-sensitive animals.

pulmonary function



More and more applications are being received for studies in this general field which have as their objective a better understanding of the effect of disease on the functioning of the lungs. Many of the projects are closely allied with surgery. Some are concerned more directly with the vascular system than with the mechanics of breathing.

Duncan A. Holaday, M.D., Columbia University College of Physicians and Surgeons, New York City. During surgery of the lung, particularly when ether is the anesthesia employed, the alkaline-acid balance of the body may be upset and acidosis develop. Dr. Holaday is experimenting with certain organic acids to gain more information about the condition and, consequently, how to prevent it and thus make pulmonary surgery safer. In connection with another phase of his investigation, he has devised a model respirator in order to study the effects of artificial respiration on the mechanics of breathing.

John W. Irwin, M.D., Microcirculatory Laboratory, Massachusetts Eye and Ear Infirmary, Boston. An extremely delicate procedure has been devised by Dr. Irwin and his associates for inserting a tube in the very small pulmonary blood vessels of animals under anesthesia in order to record changes in blood pressure before and during shock. The experiments are expected to provide data about pressure throughout the pulmonary vascular system and on changes in the arterial system during shock. So precise must every move be that a soundproof, vibration-free building is being constructed for these and similar experiments, in which several groups are cooperating.

C. J. Martin, M.D., Firland Sanatorium, Seattle, Wash. The flow of gases in and out of the different lobes of the lung is being studied in normal and in diseased patients with the aid of complicated electrical machinery. The information obtained by Dr. Martin will be particularly valuable when resection of a lobe is contemplated.

William F. Miller, M.D., Cardiopulmonary Laboratory, University of Texas Southwestern Medical School,

Dallas. Some patients with pulmonary disease develop a condition known as cor pulmonale because the flow of blood in the pulmonary blood vessels is obstructed, causing higher pressure in those vessels. Dr. Miller is studying just what happens to the blood flow in this condition and in respiratory acidosis, and also whether digitalis is or is not helpful to cor pulmonale patients.

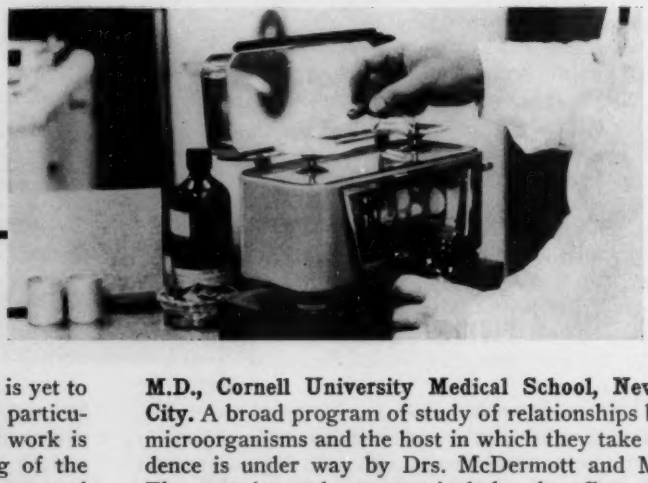
***Herrman L. Blumgart, M.D., and Myron Stein, M.D., Beth Israel Hospital, Boston.** Shortness of breath is characteristic of abnormal thyroid activity, whether high or low. The condition has been assumed to be related to changes in the circulatory system. However, Drs. Blumgart and Stein (the latter is a former NTA fellow) plan to investigate whether changes in pulmonary function play a role in this condition.

***James B. Littlefield, M.D., University of Virginia School of Medicine, Charlottesville.** When an entire lung is removed by surgery, what happens to the circulation of blood in the other lung? This is the question which Dr. Littlefield, an NTA research fellow for the year 1957-58, is attempting to study by producing "physiological pneumonectomy" in animals. Dr. Littlefield is proposing to simulate pneumonectomy by stopping the flow of blood in the vascular system of one lung by ligation, then to study the effect on the other lung.

***Arthur A. Siebens, M.D., University of Wisconsin, Madison.** If a whole lung is removed before adulthood, does the remaining lung try to compensate by changes that would not occur if full growth had been attained? This is the question which Dr. Siebens hopes to be able to answer as a result of his studies, which will be conducted with animals.

***Allan Stranahan, M.D., Albany Medical College, Albany, N.Y.** This will be a follow-up study to determine the effect on lung function of the removal of a whole lung or a part of a lung. Dr. Stranahan will attempt to follow up 100 patients who have undergone resection of a lobe or lung in order to evaluate their pulmonary status several years after surgery.

***John Mason Tyler, M.D., Lemuel Shattuck Hospital, Boston.** Although severe pulmonary emphysema is a grave medical problem today, particularly in older men, no universally applicable treatment is known. Dr. Tyler proposes to study the value of the use of different mixtures of gases in mechanical devices to aid the breathing of emphysema patients.



drug action

The "perfect" drug for tuberculosis treatment is yet to be discovered, but several drugs are effective, particularly isoniazid. How isoniazid and other drugs work is not clearly understood. A better understanding of the mode of action would lead to better use of drugs and might even uncover possible leads to a better drug.

J. Carroll Bell, M.D., Colorado Foundation for Research in Tuberculosis, Denver. One of the problems with isoniazid is that some patients metabolize it so completely that it does them little good. Other patients scarcely break it down at all and derive more benefit from it. The principal process by which isoniazid appears to be altered chemically is known as acetylation. Dr. Bell is studying not only the process by which isoniazid loses much of its value for some patients, but is also investigating whether the use of a second drug, such as PAS, will tie up the acetylation process, leaving the isoniazid free. The study is expected to provide information which will guide the clinician in deciding the dose of isoniazid for each individual patient.

Walsh McDermott, M.D., and Robert McCune, Jr., M.D., Cornell University Medical School, New York City. A broad program of study of relationships between microorganisms and the host in which they take up residence is under way by Drs. McDermott and McCune. The experimental program includes the effect of drugs on this relationship. During the year, the investigators plan to study newly developed drugs alone and in combination with isoniazid in the hope of establishing leads to more effective treatment. They also plan some studies in immunity and in the use of isoniazid as a preventive.

Lloyd J. Roth, M.D., University of Chicago, Chicago. A pharmacologist with considerable experience with atomic energy, Dr. Roth, with his associates, has learned a great deal about the way isoniazid behaves in the body by using the drug labeled with radioactive Carbon^{14}. Now they are working with a different type of tuberculosis drug, cycloserine, which is an antibiotic rather than a synthetic chemical. They are attempting to incorporate the radioactive carbon in the mold from which cycloserine is derived, instead of synthesizing it into the drug itself.

Leon H. Schmidt, Ph.D., The Christ Hospital Institute for Medical Research, Cincinnati. Monkeys are the stand-in for man in studies of numerous aspects of tuberculosis and its treatment carried on under the direction of Dr. Schmidt. One of the problems before Dr. Schmidt was the production of a subacute type of pulmonary tuberculosis resembling as closely as possible the chronic tuberculosis of man. Dr. Schmidt has recently found that certain strains of tubercle bacilli grown in a special medium can produce this type of disease, rather than the acute disease usually found in monkeys. Furthermore, he has found that age is a factor in the type of disease produced in monkeys and that older monkeys are more apt to have less acute disease. Now that he is able to produce chronic diseases in monkeys, Dr. Schmidt is proceeding to study how tuberculosis drugs act on the disease.

microbiology

Microorganisms being studied include not only *Mycobacterium tuberculosis,* but also acid-fast bacilli which show up in patients believed to have tuberculosis, but which are not tuberculosis germs. They are usually designated as atypical, or chromogenic, bacilli. In this category, too, are four studies with bacteriophage, the virus entity that attaches itself to particular strains of bacteria.

Edward N. Azarowicz, Ph.D., Johns Hopkins Hospital, Baltimore, Md. Because a phage is selective in its approach and will attach itself only to one strain of microorganisms within a given species, it can be used to identify various strains. Dr. Azarowicz is attempting to type the whole species of *Nocardia,* a fungus of the Actinomyces family, by means of phages.

Seymour Froman, Ph.D., Olive View Sanatorium, Olive View, Calif. When bacteriophages are adsorbed to tubercle bacilli, they pierce the cell and reproduce within it, eventually causing the dissolution, or lysis, of the bacillus. Dr. Froman, the first to identify bacteriophages with tubercle bacilli, is studying the effect of phage infection on the morphology of the bacillus and is continuing his classification of strains of tubercle bacilli by means of phages.

Vernon Knight, M.D., Vanderbilt University School of Medicine, Nashville, Tenn. The presence of serum from human blood in the culture medium has been observed to prevent the adsorption of phages to tubercle bacilli. Dr. Knight is attempting to identify the factor in serum responsible for this. He is also studying the effect of phages on the morphology of the bacilli and is seeking to find out whether phages are related to the virulence of tubercle bacilli, as they appear to be with some other germs.

***Margret I. Sellers, Ph.D., University of California at Los Angeles.** The chemical composition of phage is being studied by Dr. Sellers, who wants to find out whether there is any interrelationship between the chemical make-up of the virus and its ability to infect virulent acid-fast bacteria.

Max S. Dunn., Ph.D., University of California, Los Angeles. The complex chemical nature of the tubercle bacillus has long fascinated the chemist. Dr. Dunn is concentrating on the amino acids of the bacillus, particularly on glutamic acid and its possible relationship to virulence and such growth characteristics of virulence as its "cording."

William Steenken, Jr., D.Sc., Trudeau Laboratory, Saranac Lake, N.Y. If an investigator in France publishes a paper on work with the tubercle bacillus, and a scientist in California publishes on similar work but reaches a slightly different conclusion, the question arises as to whether both were working with the same strain of microorganism. As a service to investigators, the NTA maintains a "bank" of all types of tubercle bacilli from which investigators the world over may "borrow." Thus they are assured of starting their studies with identifiable strains. The bank is in the charge of Dr. Steenken, who cultures the bacilli and ships the specific strain requested to investigators anywhere.

Hilda Pope Willett, Ph.D., Duke University School of Medicine, Durham, N.C. A new amino acid isolated from a diphtheria bacterium has been demonstrated in the tubercle bacillus also. It is known as DAP. Dr. Willett, who for several years has been studying the metabolism of the tubercle bacillus, is trying to determine the importance of DAP in tubercle bacilli and whether it plays a major role in the metabolism of the bacillus.

Ernest H. Runyon, Ph.D., Veterans Administration Hospital, Sunmount, N.Y. A study of acid-fast atypical microorganisms recovered from patients in tuberculosis hospitals is being undertaken by Dr. Runyon. In cooper-

ation with the Laboratory Committee of the ATS, Dr. Runyon is maintaining a culture bank of these bacilli, and is attempting to classify the bacilli by pigmentation, morphology, virulence, and other properties.

Donald W. Smith, Ph.D., University of Wisconsin, Madison. On the assumption that microorganisms which are biologically distinct may also be chemically distinct, Dr. Smith is using modern techniques to study the chemical nature of various strains of acid-fast bacilli, including the atypical. From Dr. Smith's work may come a simple chemical method of distinguishing between various strains of bacilli recovered from patients.

clinical experience

The studies under this classification are by physicians who are dealing directly with patients. Three of the studies deal with children or young girls; two are studies on extrapulmonary tuberculosis; and two are concerned with emphysema, a common disease of the lung which is not tuberculous in origin.

Geoffrey L. Brinkman, M.D., Henry Ford Hospital, Detroit, Mich. Dr. Brinkman is making a study of the incidence of diffuse obstructive emphysema in an industrial plant—in this instance, the Rouge Plant of the Ford Motor Company. The grant is for funds to purchase the necessary chest X-ray films.

Mrs. Shirley H. Ferebee, Division of Special Health Services, Department of Health, Education, and Welfare. Shortly after isoniazid came into use, several pediatricians noticed that children with primary tuberculosis treated with this drug did not develop serious complications. Was this because of some special attribute of the drug, which streptomycin and other drugs did not possess? To find the answer, the Public Health Service coordinated a study among pediatricians in 33 centers throughout the continental United States, San Juan, Mexico City, and Toronto. The study is being conducted on a controlled basis, with some children with primary tuberculosis being given isoniazid and some a placebo. Preliminary reports indicate that statistically significant fewer complications have occurred among the children receiving isoniazid. Although the major funds for this project are from the National Institutes of Health, grants from the NTA and affiliated associations have been essential to the conduct of the study.

Edith M. Lincoln, M.D., New York University-Bellevue Medical Center, New York City. Back in 1930 Dr. Lincoln began making a study of what happened in later years to children diagnosed at the Bellevue Chest Service as having primary tuberculosis. By 1940 Dr. Lincoln had records on 1,000 such cases and was following them up until each child reached the age of 25. Valuable information concerning the natural course of tuberculosis has been obtained through this study. Furthermore, in 1947 Dr. Lincoln began the follow-up of another series—children treated with drugs. Not only will results from this second group serve as a comparison for the other, but the follow-up will also reveal valuable data on the long-term effect of chemotherapy.

Soledad Morales, M.D., New York University-Bellevue Medical Center, New York City. In the study of the natural course of tuberculosis in children, Dr. Edith Lincoln, of Bellevue, observed that if children who had had primary tuberculosis broke down with second infection it was usually at the time of adolescence. Some of the factors that may influence breakdown in adolescent girls are being investigated by Dr. Morales. In regular checkups of young girls who have healed primary tuberculosis, Dr. Morales is studying in particular the role of the glands and metabolism in disease at adolescence.

Julia M. Jones, M.D., Chest Service, Bellevue Hospital, New York City. A study of tuberculosis other than pulmonary is being made by Dr. Jones by following the clinical, pathological, and bacteriological course of extrapulmonary disease under various methods of treatment.

John K. Lattimer, M.D., Columbia University College of Physicians and Surgeons, New York City. A urologist, Dr. Lattimer has for many years been studying the treatment of renal tuberculosis in patients in the Veterans Administration Hospital in the Bronx. With the aid of the NTA grant, he has expanded his study to include women and children with genitourinary tuberculosis. Dr. Lattimer has reported, from his earlier studies, that the use of three drugs (isoniazid, streptomycin, and PAS) frequently obviated the need for surgery in tuberculosis of the kidney. He is now trying a regimen that substitutes cycloserine for streptomycin, which is given by injection, to use drugs which can be given by mouth.

Charles A. Werner, M.D., Infectious Disease Laboratory, Bellevue Hospital, New York City. Emphysema is a trying condition in which air gets "caught" in the lung and causes great discomfort. Treatment has ordinarily been through medicines and mechanical aid in helping the lung expel the air causing pressure. Dr. Werner is directing a clinical study to test the efficacy of various drugs in preventing the progression of emphysema.

other applications

The following applications have been approved, but funds are not yet available for the grants. Additional support for medical research will make possible grants to these investigators. If the funds are earmarked for one of the other projects, the money thus released will be used for one of the applications below.

***Ernest O. Attinger, M.D., Boston City Hospital Lung Station, Boston.** (Pulmonary function) A patient with lung disease may be able to go through the mechanical process of breathing, but at great cost to his system as a whole. Dr. Attinger proposes to study whether the actual work of respiration in patients with pulmonary disease leaves enough oxygen for the other needs of the body. Believing that reduction of respiratory work rather than stimulation of respiration is important in patients with pulmonary disease, Dr. Attinger hopes to devise a method for accomplishing this.

***Egons Darzins, M.D., Anoka State Hospital, Anoka, Minn.** (Microbiology) Ever since it has been definitely known that the tubercle bacillus was the causative agent of tuberculosis, scientists have tried to probe the secret of the virulence of the microorganism. Dr. Darzins believes that the desoxyribonucleic acid (a component of the genes) structure of the bacillus may be related to its pathogenicity and wishes to investigate this possibility.

Harold L. Israel, M.D., Graduate School of Medicine, University of Pennsylvania, Philadelphia. (Clinical) A disease of unknown etiology, sarcoidosis may mimic other diseases of the lung, such as tuberculosis or cancer. Dr. Israel is engaged in a long-range study of the epidemiology of sarcoidosis and is also attempting to develop a skin test that will reveal its presence. Having observed that a number of patients with sarcoidosis have a history of use of photographic processing materials, Dr. Israel and associates are at present employing chemicals used in photographic processing in a skin test.

***Karl E. Karlson, M.D., State University of New York College of Medicine, Brooklyn, and U.S. Naval Hospital, St. Albans, N.Y.** (Pulmonary function) The compliance, or elastic recoil, of a single lung during an operation for removal of small lesions or tumors is the subject proposed by Dr. Karlson for study. Such data are not now available. Dr. Karlson wishes to correlate data on changes in compliance under the above conditions with other factors in pulmonary function and cardiac output.

***Herbert McKennis, Jr., Ph.D., Medical College of Virginia, Richmond.** (Drug action) Most of the studies of the fate of isoniazid have been directed at how the body uses isonicotinic acid. Dr. McKennis proposes to attempt to determine how the body uses the drug, with particular attention to the hydrazine part. (Chemically, isoniazid is isonicotinic acid hydrazide.)

***Peter C. Luchsinger, M.D., Georgetown University Medical School, Washington, D.C.** (Pulmonary function) Many factors come into play in the function of the lung in providing oxygen for the body and expelling carbon dioxide. Dr. Luchsinger proposes to study how disease of the lungs affects the flow of oxygen from the air sacs of the lung to the blood capillaries in the lung. From the data obtained, Dr. Luchsinger hopes to clarify the importance of changes in blood flow in patients with low diffusing capacities—that is, patients in whom the flow of oxygen is subnormal.

***Stanford K. Sweany, M.D., Veterans Administration Research Hospital, Chicago.** (Pulmonary function) A study of the diffusing capacity of people with severe pulmonary emphysema is proposed by Dr. Sweany. Using methods that enable him to differentiate between the two major factors in pulmonary diffusion—the role of the membrane lining the air sacs and the function of the volume of blood in the pulmonary capillaries—Dr. Sweany plans to make a comparative study of the patients in their usual condition, during periods of stress following secondary infection, and after recovery.

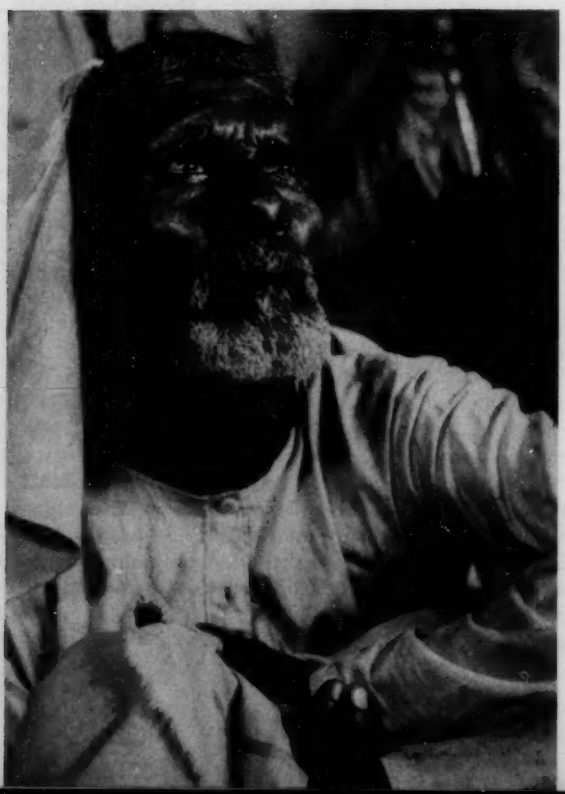
Lawrence E. Wood, M.D., University of Kansas Medical Center, Kansas City, Kan. (Epidemiology) A study over the past 10 years of the tuberculin test as a case-finding tool is being continued by Dr. Wood. The tuberculin test is being used to compare the infection rate of children in the eighth and ninth grades with children in kindergarten and the first grade; to determine the frequency of conversion by the time the higher grades are reached; to determine the prevalence of cases of tuberculosis among children in the higher grades and to find their household contacts; and to determine the cost of this method of case finding.

***George W. Wright, M.D., St. Luke's Hospital, Cleveland, Ohio.** (Pulmonary function) Information contributed to scientific knowledge as the result of the first medical research grant awarded by the NTA will be the starting point for studies proposed by Dr. Wright. The physiologist plans to construct a three-dimensional model of a lung, duplicating tissue, blood vessels, etc., and to show the changes brought about in the lung as the result of diffuse, obstructive emphysema. Dr. Wright will start with the techniques used by the late Dr. William Snow Miller, who received the first NTA grant for his study of the lung, and will also employ more recently developed techniques.

***Robert R. Wright, M.D., University of California Medical School, San Francisco.** (Clinical) A study of the course of pulmonary emphysema is proposed by Dr. Wright. He hopes to determine from autopsy material and animals whether emphysema is a degenerative disease and whether conditions which cause coughing aggravate it.

At Madras, India, a World Health Organization tuberculosis team is experimenting with isoniazid in a mass chemoprophylaxis campaign. Here a tuberculosis patient swallows an isoniazid tablet while members of his family look on.

Hope for the future is expressed in the eyes of this patient waiting examination at the Patna TB Control Demonstration and Training Centre, Bihar State, India.



World Healt

The World Health Organization is celebrating its tenth anniversary this year, in Minneapolis, simultaneously with the eleventh regular session of its governing body, the World Health Assembly, May 26-June 14.

Conceived at an International Health Conference called by the United Nations in 1946, and officially established in 1948, WHO has grown from 26 member nations to 88, which do not necessarily also belong to the UN.

WHO defines health as a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity. The organization works to prevent infectious diseases (tuberculosis, malaria, etc.) and to train health workers. It gives technical assistance to improve sanitary conditions in more than a hundred countries, warns of outbreaks of epidemic disease, coordinates research, and recommends international standards for drugs and vaccines.

WHO does not itself directly undertake or control medical and health programs in member countries. The national health services carry out the field programs for which international assistance has been provided. During 1958, nearly 700 projects assisted by WHO will be in operation in 112 countries and territories.

Tuberculosis, leprosy, and malaria are prime targets in WHO's global attack upon disease. *Top:* A little boy who lives in a refugee camp on the outskirts of Saigon, Viet-Nam, is vaccinated with BCG by a member of a WHO team. *Center:* In Mexico, members of "spray teams" travel by motor and by horseback throughout the country in an organized drive to eradicate malaria. After spraying each house, the team member inspects it to make sure that all the mosquitoes' hiding places have been covered by the insecticide. *Bottom:* Thanks to an intensive anti-leprosy campaign started in Burma in 1952, these young leprosy patients were found in the early stages of the disease and have a good chance of a complete cure.

and the WHO

With headquarters in Geneva, WHO has a staff of about 1,000 professionals of 54 nationalities. Its budget, contributed by member nations, is $13,500,000 for 1958. The World Health Assembly is made up of delegations from each of the member nations, and decides the organization's policies, program, and budget.

Among the nongovernmental agencies which are officially recognized by WHO and which are permitted to send delegates to the Assembly is the International Union Against Tuberculosis. Dr. James E. Perkins, managing director of the National Tuberculosis Association, is the Union's delegate at this year's meeting.

Because of the importance of WHO in improving the health of citizens throughout the world, a National Citizens Committee for the World Health Organization has been established in the United States. It is supported by individual citizens and by national health agencies, including the NTA. Dr. Perkins is currently president of the committee.

For those interested in reading more about WHO's activities, *Doctors of the World*, by Dr. Murray Morgan, just published by Viking Press, describes the efforts of hundreds of doctors and health workers in fighting disease.

Iowa Chart Gives All County TB Data

The Iowa Tuberculosis and Health Association has developed an annual County Statistical Chart, which shows all reported tuberculosis data for the state during the year. Among the facts included for each of the 99 counties are number of tuberculosis deaths, death rates, number of patients treated at home and in various types of hospitals, number of new cases reported, new case rates, Seal Sale per capita, number of public health nurses.

This easy-to-read, one-page chart is of value not only to those directly concerned with tuberculosis control, but also for educating the public about the local and state tuberculosis problem. Any association interested in developing a similar chart may obtain a copy from the Statistical Division, Iowa Tuberculosis and Health Association, 2124 Grand Ave., Des Moines 12, Iowa.

OVR Rehabilitates Record Number in 1957

A record number of 71,570 disabled persons were returned to work through the state and federal agencies of the Office of Vocational Rehabilitation, and through private agencies which received some OVR support, during the fiscal year ending June 30, 1957.

It is estimated that the 70,939 persons rehabilitated through the state-federal program will increase their annual earnings from $18.9 million to about $137.6 million in their first full year of employment. Some 3,500 entered the professional fields of education, medicine, and engineering; about 8,700 went into skilled trades; and 6,100 went into agriculture. Most of the others are in managerial, sales, or service jobs or in unskilled work.

About 53,000 of those rehabilitated were unemployed when they began receiving services; some 14,000 had been receiving public assistance; and the others were in part-time, unsafe, or unsuitable work.

X-rays to Music

BECAUSE poverty forces many Indians in Omaha, Neb., to live in the same skid row areas as homeless white men, case-finding programs there must appeal to both groups. After months of effort to win the confidence of the Indians (which included running a three-day powwow), and with the help of mission directors, saloon keepers, and official public health agencies, the Nebraska Tuberculosis Association found the solution: a mobile X-ray unit accompanied by a 12-piece band each evening of the survey, with free refreshments for everyone X-rayed. The result: Every one of the Indians in the area had a chest X-ray.

Successful Demonstrations in Wayne County

Three demonstration projects started by the Tuberculosis and Health Society of Wayne County (Detroit) in recent years, to provide new services for the tuberculous, have been taken over by official agencies. The first was a health education coordinator working on patient, family, and visitor education at Herman Kiefer Hospital, who was placed on the city payroll a few years ago. Then, the six-member vocational rehabilitation department at Kiefer and Maybury hospitals, a demonstration project of the Society for five years, was made an official part of the services provided by these hospitals.

Most recently, three members of the Society's four-member team of medical social workers at Herman Kiefer Hospital were transferred to the Department of Health payroll. In addition, two case workers from the city and county departments of welfare will work with the staff. The Society will continue to pay the salaries of the remaining case worker and of one new case worker.

SCIENTISTS AT WORK

Twelve men—and one woman—sat down in a hotel room in New York late in February for a special sort of jury duty. Their task was to evaluate the work of peers, and, in so doing, they became the participants in a stimulating scientific conference.

It was the annual winter meeting of the Committee on Medical Research of the American Trudeau Society. The committee was charged with responsibility for reviewing applications for medical research grants from the National Tuberculosis Association for the year beginning July 1 and extending through June 30, 1959.

It was a responsibility no member of the committee took lightly. Each had received in advance copies of the 61 applications and had studied them carefully before coming to the meeting. The applications contained information regarding the purpose of the research, where it would be conducted and by whom, and a detailed budget of anticipated expenditures.

The meeting was called to order by Dr. William R. Barclay, of Chicago, chairman of the Committee on Therapy, who presided in the absence of Dr. Robert H. Ebert, chairman of the research committee, who was unable to be present.

Applications were taken up in alphabetical order, and discussion was opened by a member of the committee who had been asked in advance to present a critique of the work for which Christmas Seal funds were requested. In each instance, the "homework" had been assigned according to the particular interest of the committee member in the applicant's field of research.

The opening remarks, however, were but the take-off for a lively discussion in which microbiologist questioned immunologist, surgeon exchanged data with physiologist, pathologist supplemented points made by internist. There was no rubber stamp in the room. The inquiring mind of the scientific investigator looked at the application from every angle and voted approval only when satisfied with the worth of the project.

It was thus a tribute to the caliber of the applications that by the end of the second and final day of the meeting, 48 of the 61 applications had been approved. A brief description of each of these 48 projects can be found on pages 85-91.

Throughout the committee's deliberations, Dr. Leonard Karel, of the National Institutes of Health, U. S. Public Health Service, was present to answer any questions about related grants from NIH. Other guests present included Dr. William M. Morgan, president of the NTA; Dr. Theodore L. Badger, president of the ATS; Dr. Raymond C. McKay, ATS representative on the NTA Committee on Social Research; and Dr. William B. Tucker, director of the Tuberculosis Service, Veterans Administration, and chairman of the ATS Committee on Medical Education.

In addition to Dr. Barclay, members of the committee present were Dr. Martin M. Cummings, of Washington, D.C.; Dr. Nicholas D'Esopo, of West Haven, Conn.; Dr. Giles Filley, of Denver, Colo.; Dr. Irving Gordon, of Los Angeles, Calif.; Dr. Gladys Hobby, of Brooklyn, N.Y.; Dr. Esmond R. Long, of Pedlar Mills, Va.; Dr. Max B. Lurie, of Philadelphia, Pa.; Dr. Sidney Raffel, of Los Angeles; Dr. Emil Rothstein, of West Newton, Mass.; Dr. Leon H. Schmidt, of Cincinnati, Ohio; Dr. Norman Wilson, of Brookline, Mass,; and Dr. Emanuel Wolinsky, of Cleveland, Ohio. Dr. Edward Blomquist, Washington, D.C., also a member of the committee, could not attend.—A.S.F.

The Cover

Rabbits are infected with air-borne tubercle bacilli in a special apparatus at the Henry Phipps Institute, Philadelphia, where Dr. Max Lurie is using the rabbits in studies on resistance to tuberculosis. A report on Dr. Lurie's investigations appeared in this column in the March *Bulletin*.

Jury duty: The ATS Committee on Medical Research meets to discuss and act on the applications for NTA research grants for the year beginning July 1, 1958.

Henry Phipps Institute to Construct New Plant

The Henry Phipps Institute for the Study, Treatment and Prevention of Tuberculosis, of the University of Pennsylvania, is arranging to move from its present location in downtown Philadelphia to a new building to be constructed in West Philadelphia, adjoining the new West Philadelphia Health Center.

Proceeds from the sale of the present site and a recent gift to the university of $53,500 from the family of the late Henry Phipps will be used to construct the new facilities. A portion of the institute's new research laboratories will be built through a U.S. Public Health Service grant of $400,000. The institute will undertake field studies of disease among large population groups. Tuberculosis studies will be continued, but emphasis will be placed on chronic diseases.

PEOPLE

Walter B. Furbush, who has been administrative assistant for the past two years to Dr. James E. Perkins, managing director of the National Tuberculosis Association, has been appointed associate director of the NTA Personnel and Training Division. Mr. Furbush had formerly been training administrator for the NTA and executive secretary of the Cortland County (N.Y.) Tuberculosis and Health Association and of the Albany County (N.Y.) Tuberculosis Association.

Charles C. Macnamara, formerly executive director of the Contra Costa (Calif.) Tuberculosis and Health Association, has been appointed executive secretary of the Oahu (Hawaii) Tuberculosis and Health Association. Mr. Macnamara succeeds **Miss Bess Hammer,** who has joined the Arizona Tuberculosis and Health Association as program associate.

George W. Ranta, formerly Christmas Seal director of the Northern Worcester County (Mass.) Public Health Association, has been appointed executive director of the Berkshire County (Mass.) Tuberculosis Association.

Mrs. Naomi Kalajan, formerly health education counselor and supervisor of field training for the Los Angeles County Tuberculosis and Health Association, has been appointed executive director of the Greater Phoenix (Ariz.) Tuberculosis Association.

Graydon Dorsch has resigned as executive director of the Denver Tuberculosis Society, a position he had held for the past ten years. Mr. Dorsch plans to devote his full time to writing.

William Pfeifer, formerly on the staff of the Indiana Tuberculosis Association, has been appointed executive secretary of the Heart of America (Kansas City, Mo.) Tuberculosis Association.

Winston S. Bailey, who has been business manager and Seal Sale director of the Queensboro (N.Y.) Tuberculosis and Health Association for the past year, has been promoted to assistant executive director of the association.

Dr. Norvin C. Kiefer, chief medical officer of The Equitable Life Assurance Society, has been elected president of the National Health Council. Re-elected as one of the two vice presidents was **Dr. James E. Perkins,** managing director of the National Tuberculosis Association.

THE AMERICAN REVIEW OF TUBERCULOSIS AND PULMONARY DISEASES was honored recently to receive a request for a subscription to its publication from internationally renowned missionary surgeon and philosopher **Dr. Albert Schweitzer.**

Noble J. Swearingen, who has been chief of legislative information for the National Tuberculosis Association for the past five years, has joined the American Public Health Association as director of its southern office and staff representative of its Public Policy and Legislation Committee. Mr. Swearingen will be located in Washington, D. C., and will also serve as consultant to the NTA on legislative matters. An appointment will be made to cover the activities of the legislative unit in the national office.

Harold N. Weiner has been appointed executive director of the National Publicity Council for Health & Welfare Services, succeeding **Irving I. Rimer,** who has joined the American Cancer Society as coordinator of the Department of Information. Mr. Weiner was formerly director of fund raising and public relations for the Connecticut Association for Mental Health and acting executive director of the Tuberculosis and Health Association of the New Haven Area.

George Weberling has been appointed executive director of the La Salle County (Ill.) Tuberculosis Association, succeeding **Clifford Gregor.** Mr. Weberling was formerly health director for the association and executive secretary of the Kankakee County (Ill.) Tuberculosis Association.

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